Remifentanil and Fentanyl Use and the Liver Function Tests

Remifentanil ve Fentanil Kullanımı ve Karaciğer Fonksiyon Testleri

Remifentanyl and Fentanyl Use and LFT/ Remifentanil ve Fentanil Kullanımı ve KCFT

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Özet

Amaç: Günübirlik hastalarda fentanil ve remifentanil ile yapılan total intravenöz anestezi sırasında postoperatif karaciğer fonksiyonları karşılaştırmaktı. Gereç ve Yöntem: Elli erişkin hasta anestezi rejimlerine göre rastgele (n = 25) iki gruba ayrıldı; remifentanil (15 µg / kg / saat, grup R) veya fentanil (1.5 µg / kg / saat, grup F). Propofol (2.5mg/kg) ve rokuronyum bromid (0.5 mg / kg) verildikten sonra, hastalar entübe edildi. Propofol 9mg/kg/saat infüzyon verilerek anestezi devamlılığı sağlandı. Ameliyat öncesi ve sonrası karaciğer fonksiyon testleri, hemodinami, anestezik gereksinimleri ve derlenme süreleri kaydedildi. Bulgular: Derlenme süresi R grubunda, grup F'ye göre anlamlı olarak daha düşüktü (8.6 ± 1.2 dk ve grup F 3.5 ± 0.5 dk ve R) (p = 0.0001). Postoperatif yüksek dansiteli lipoprotein, total protein ve alkalin fosfataz her iki grupta da anlamlı olarak düşüktü (96.3±31.9; 6.1±1.4; 186.8±73.5 grup F'de, 94.8±29.6; 6.2±1.2; 163.7±68.5 grup R'de) (sırasıyla p=0.003, p=0.0001 ve p=0.002 idi). Postoperatif protrombin zamanı her iki grupta da belirgin olarak daha uzundu (Preoperatif'e karşılık postoperatif değerler grup F'de: 13.6±0.8'e karşılık 14.5±1.08 (p=0.001) ve grup R'de: 13.9±0.9'e karşılık 19.6±25.0) (p=0.001). Sonuç: Fentanil ve remifentanil KCFT, hemodinami, anestezik gereksinimleri ve ameliyat sonrası ağrıyı azaltmada benzer etkilere sahiptir. Ancak, grup R'de, derlenme süresi F grubuna göre daha kısa idi.

Anahtar Kelimeler

Karaciğer Fonksiyon Testleri (KCFT); Remifentanil; Fentanil; Total İntravenöz Anestezi (TİVA)

Abstract

Aim: To compare the postoperative hepatic functions during total intravenous anesthesia with fentanyl and remifentanil in outpatient settings. Material and Method: Fifty adult patients were randomly allocated to one of two anesthetic regimens (n=25) and were received remifentanyl (15 µg/kg/h; group R) or fentanyl (1.5 µg/kg/h; group F) intravenously. After giving propofol (2.5 mg/kg) and rocuronium bromide (0.5 mg/kg), patients were intubated. Propofol was continued to infuse at 9 mg/kg/h rate. The preoperative and postoperative liver function tests, haemodynamic parameters, anesthetic requirements, and recovery times were recorded. Result: Recovery times in group R was significantly lower than in the group F (8.6±1.2 min and 3.5±0.5 min in group F and R) (p=0.0001). The postoperative values of high density lipoprotein, total protein and alkaline phosphatase were significantly lower than the postoperative values in group F and R (96.3±31.9; 6.1±1.4; 186.8±73.5 in group F, 94.8±29.6; 6.2±1.2; 163.7±68.5 in group R) (p=0.003, p=0.0001 and p=0.002, respectively). The postoperative prothrombin time was significantly longer than the preoperative values in groups F and R (Preoperative and postoperative values in group F: 13.6±0.8/14.5±1.08 (p=0.001) and in group R: 13.9±0.9/19.6±25.0) (p=0.001). Discussion: Fentanyl and remifentanil have a similar effect on the LFT, haemodynamics, anesthetic requirements, reducing the postoperative pain. However, in group R, recovery time is shorter than in group F.

Keywords

Liver Function Tests (LFT); Remifentanil; Fentanyl; Total İntravenous Anesthesia (TIVA)

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Introduction

Abnormal liver function tests (LFT) are frequently detected in asymptomatic patients since many screening test panels are being routinely performed now [1].

The effects of various volatile anesthetics on major organs have been extensively evaluated. However, the impact of fentanyl and remifentanil under total intravenous anesthesia (TIVA) has been less extensively investigated than that of volatile anesthetic agents. Propofol has also been reported to show a safe pharmacological profile in the presence of hepatic impairments; furthermore, its clearance and elimination is unaffected by hepatic dysfunction [2].

To prevent the stress and anxiety, we should develop an effective, safe and careful analgesic regimen during TIVA [3-5]. Short-acting opioids (eg, fentanyl, remifentanil) are appropriate agents to decrease the cardiovascular effects of sympathetic nervous system stimulation and prevent the sympathetic response to laryngoscopy [6-8].

This double-blind, randomized study was conducted to compare the efficacy and safety of remifentanil and fentanyl as the analgesic agents in LFT, postoperative analgesia, haemodynamics, recovery time in adult patients under TIVA in outpatient settings.

Material and Method

After obtaining the approval of the Institutional Ethics Committee at Gaziantep University and written informed patients' consent, 100 ASA (American Society of Anesthesiologists) physical status I-II patients aged 22-54 years were scheduled for day case surgery, comprising 14 inguinal hernia and 36 breast biopsy under total intravenous anesthesia (TIVA). Patients were enrolled in this double-blind study from May through October 2009.

Patients with heart blocks, heart failure, hepatic disease, musculoskeletal disease, hepatic failure, psychiatric disease, neurological disease, or those who had BMI> 30, or who used to be or were smokers and received analgesics or sedatives within the previous 24 hours were excluded from the study. In addition, patients with a history of allergy to opioids, viral hepatid and other liver disease, propofol, or alcohol/drug abuse were excluded from the study. None of the patients was premedicated with any drug. Patients were randomized into two groups using a computer generated random number table. Patients were received 15 µg/kg/h remifentanyl (ULTIVA, Glaxo Smith Kline, Australia). (group R, n=25) or 1.5 µg/kg/h fentanyl (FENTANYL CITRATE, Abbott, Beerse, Belgium) (group F, n=25) intravenously (iv) for maintaining the analgesia. The study drugs including fentanyl and remifentanyl were prepared with 0.9% NaCl in unlabeled 20 ml-syringes. After the patients had been taken to the surgery room, standard monitors including electrocardiography (lead II), non invasive blood pressure (MAP) and peripheral oxygen saturation measurements (Drager Cato PM 8040, Lubeck, Germany) were initiated. A 20-gauge cannula was inserted into a vein in the dorsum of the hand and isotonic saline solution was infused at a rate of 5-7 ml//kg/h. Both drugs were started to administer at induction period.

After preoxygenation, anesthesia was induced with iv propofol (Propofol 1% Fresenius, 10 mg/ml) (2.5 mg/kg) and remifentanyl or fentanyl and maintained with 9 mg/kg/hour of propofol and the gas mixture of 50% oxygen in 50% air. After the loss of consciousness, rocuronium bromide (Esmeron, Organon, Oss Holland) (0.5 mg/kg) was injected and patients were intubated. Dose adjustments were made at 10 min intervals according to MAP an HR. Mean arterial blood pressure and heart rate (HR) were recorded at baseline and intraoperative 5,10,15,20,30,45,60,90,120,150. min. Adverse events such as bradycardia, hypotension, nausea, vomiting were recorded. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total protein (TP) total bilirubin (TB), prothrombin time (PT), partial thromboplastin time (APTT), lipoproteins (HDL, LDL), blood glucose (BG) were investigated during the preoperative and postoperative periods.

Normal ranges of LFTs were accepted as below: Alanine transaminase ALT: 0–45 IU/l; AST: 0–35 IU/l; Alkaline phosphatase ALP: 30–120 IU/l; TB: 2–17 µmol/l; PT: 10.9–12.5 sec; TP: 6-8 gr/dl; APTT: 26-37.2 sec; HDL: >35 mg/dl; LDL: <130 mg/dl; BG: 70-110 mg/dl. [1, 9-11].

An independent blind anesthesiologists administered the drugs

Table 1. Demographic Characteristics, Recovery Times, Duration of Anesthesia, The Consumption of Anesthetics, VRS at postoperative 5. min, 30. min and at 60. min of the Groups.

	Group F (n= 25)	*Group R(n= 25)*	*p*
Age (yr)	40.9±14.1	38.0±16	NS
Weight (kg)	73.5±14.5	70.0±14.2	NS
Gender (M/F)	12/13	7/18	
Recovery Times (min)	8.6±1.2	3.5±0.5*	0.0001
Duration of Anesthesia (min)	211.0±135.0	213.0±10.6	NS
The Consumption of Anesthetics (propofol, mg)	162.0±31.2	154.0±34.2	NS
VRS at postoperative 5. min	3 (2-4)	2 (2-5)	NS
VRS at postoperative 30. min	5 (3-6)	4 (3-4)	NS
VRS at postoperative 60.min	7 (6-8)	7 (4-8)	NS

* p< 0.05 when compared with group F

Data are presented as mean ± SD or n or median (minimum-maximum).

Table 2. The Liver Function Tests (LFT) of the Groups.

	Group F (n=25)		*Group R (n=25)*		*p*
	preop.	postop.	preop.	postop.	
Glucose (mg)	99.0±29.7	114.7±29.3*	93.2±20.2	108.8±32.3*	0.003
AST	20.8±5.7	21.7±8.3	23.6±9.5	21.7±8.4	NS
ALT	19.3±8.4	20.6±10.9	22.4±14.8	19.7±11.5	NS
ALP	217.1±75.7[&]	186.8±73.5	191.5±57.8[&]	163.7±68.5	0.002
Total protein	7.5±0.5[&]	6.1±1.4	7.7±0.6[&]	6.2±1.2	0.0001
Total bilirubin	0.4±0.2	0.5±0.1	0.5±0.3	0.6±0.3	NS
PT	13.6±0.8	14.5±1.08*	13.9±0.9	19.6±25.0	0.001
INR	1.0±0.07	1.1±0.1*	1.06±0.08	1.1±0.1*	0.001
APTT	30.9±3.6	29.2±3.2	30.4±2.5	29.6±5.9	0.03
Amylase	58.1±15.8	52.1±19.1	61.7±14.9	59.8±15.6	NS
TG	131.3±62.8	123.6±56.2	139.4±56.2	129.6±42.6	NS
Cholesterol	142.4±45.1	133.6±46.4	143.0±50.4	144.3±46.4	NS
LDL	43.7±5.6[&]	35.1±9.4	44.6±10.9	38.8±11.1	0.0001
HDL	100.1±28.2[&]	96.3±31.9	103.1±34.6[&]	94.8±29.6	0.003

*p< 0.05 when the postoperative values were higher than the preoperative values.

[&]p< 0.05 when the preoperative values were higher than the postoperative values.

and another one collected the data. Infusion of propofol and both opioid drugs was discontinued 5 min before ending the operation and anesthesia. We recorded recovery time as the time from the end of propofol infusion until verbal communication. We assessed the postoperative pain score via VRS at 5th, 30th and 60th minutes after recovery time. The evaluation was performed using a 10 point VRS scale (0= no pain and 10= worst pain imaginable). The patients were treated when the systolic arterial blood pressure was below 90 mm Hg and heart rate was below 50 beats/min.

Statistical Analysis

For the statistical evaluation of the findings obtained in the study, SPSS (Statistical Package for Social Sciences) for Windows 15.0 program (Chicago, USA) was used. Data are expressed as means±SD or as the number of patients or median (min-max) whenever appropriate. The results were evaluated at 95% confidence interval, and significancy was evaluated at $p<0.05$ level. The relationships among the qualitative datas such as patient characteristics, demographic data, VRS were analyzed using Kruskal-Wallis Variance Analysis test and Chi-Square test. The intraoperative haemodynamics, LFT and recovery time were evaluated by one-way analysis of variance (ANOVA). The preoperative and postoperative MAP, HR and LFT were evaluated by Paired Sample t Test. We did not performe the G power analysis.

Results

No statistically-significant difference was recorded between the groups in terms of demographic characteristics and operation time. Duration of anesthesia and the requirement of anesthetic drugs were similar between the groups (Table 1).

Recovery times in group R was significantly shorter than in group F (3.5±0.5min; 8.6±1.2min) (p=0.0001) (Table 1). The verbal rating scale (VRS) in groups R and F were similar at postoperative 5th, 30th and 60th min (Table 1). No hemodynamic adverse effect (such as hypotension, hypertension, bradycardia or arrhythmia) was observed between the groups.

The preoperative values of HDL, total protein and ALP were significantly higher than the postoperative values in groups F and R (96.3±31.9; 6.1±1.4; 186.8±73.5 in group F, vs. 94.8±29.6; 6.2±1.2; 163.7±68.5 in group R) (p=0.003, p=0.0001 and p=0.002 respectively)(Table 2). The postoperative PT was significantly longer than the preoperative values in groups F and R (Preoperative and postoperative values in group F: 13.6±0.8/14.5±1.08 (p=0.001) and in group R: 13.9±0.9/19.6±25.0) (p=0.001).

Although the adverse effects were not significant, during the study, two patients in group F, two patients in group R experienced nausea and vomiting.

Discussion

The usage of remifentanil and fentanyl during TIVA with propofol caused mild liver impairment without serious adverse effects and supplemental anesthetics requirement. Contrary to fentanyl, remifentanyl showed an effective and rapid recovery from anesthesia.

Opioids produce their therapeutic effects by acting as agonists at μ and/or Κ opioid receptors [18]. For the risk for accumulation and delayed recovery with opioid agents, opioid dose was minimized in this study. Remifentanil, which is used during induction and maintenance of general anaesthesia is independent of infusion duration [19]. It has an onset of action of about 1 min in the present study. The organ independent metabolism is one of the most significant advantages of remifentanil in patients with liver impairment. Gupta et al., [20] reported that remifentanil was observed as an effective drug in patients undergoing short, painful procedures. Fentanyl's effects begin within 2 to 3 minutes of administration; its duration of action is 30 to 60 minutes [7]. Providing effective analgesia for patients in the postoperative period is important in controlling pain, relieving agitation and anxiety, and maintaining patient comfort. TIVA, performed with IV drugs which have more rapid onset and shorter recovery profiles, is available. Among these iv drugs, propofol is the most commonly used iv anesthetic agent to produce adequate pain control [21], and it is commonly administered with an opioid such as remifentanil [22]. Many known benefits of TIVA include reduced postoperative pain, less postoperative nausea and vomiting, and, most interestingly, less risk of organ toxicity such as hepatic toxicities [23]. Recently, TIVA has been widely used during various types of surgical procedures [22]. However, the influence of IV anesthetics on hepatic functions is not well established; therefore, it was our goal to determine the effects of TIVA with propofol-remifentanil or propofol-fentanyl on postoperative hepatic functions and to compare their relative safety.

Recovery times in group R was significantly shorter than in group F. Soltész et al., [24] also reported faster recovery when using remifentanil than sufentanil. Unlike existing opioids, remifentanil is rapidly metabolized by nonspecific blood and tissue esterases [25] into a clinically inactive metabolite. The difference of recovery time may be the result of the difference between duration of the drugs.

The verbal rating scale (VRS) in groups R and F were similar at postoperative 5, 30, 60th min. The stress and anxiety associated with acute postoperative pain can be prevented through careful selection of an effective analgesic regimen.

Fentanyl is most often used in the emergency settings and several randomized controlled trials. In these processes, fentanyl has been found to be effective at attenuating rises in blood pressure and heart rate during rapid sequence intubation [7]. In addition, both fentanyl and remifentanil had similar analgesic efficacy for the median total dose of propofol administered to patients during TIVA. The similarity in the anesthetic requirement, MAP and HR data may show that remifentanil and fentanyl provide a similar and acceptable degree of analgesia and haemodynamic stability during TIVA. There was no statistically significant difference between the 2 groups in the incidence of drug related adverse events (2 patients in group F, 2 patients in group R experienced nausea and vomiting). These adverse events are generally typical of potent μ opioid agonists and with the postsurgical setting.

The preoperative values of HDL, total protein and ALP were significantly higher than the postoperative values in groups F and R. As the postoperative decrease of HDL, total protein and ALP and the elevation of PT were not in a clinically important level, we may evaluate this as a minimal liver impairment. The healthy population showing normal range of LFT may have any subclinical liver disease. In addition, Lee et al., [26] reported that almost any medication can alter liver enzyme levels. The common causes include nonsteroidal antiinflammatory drugs, antibiotics, antiepileptic drugs, antituberculous drugs and statins [27]. Predictable drug reactions are dose-dependent. In addition, the increase in serum ALT correlates with body mass index (BMI) [16, 17, 28]. Anesthetic and analgesic drugs may have been the result of this change between the LFT. Liver enzyme alterations

suggest repeating tests as a first measure in order to rule out laboratory error. Restricted physical activity and hospital diet and hemodilution may be other possible explanations for the decrease in HDL, ALP and total protein. ALP originates mainly from two sources: Liver and bone [29] and the enzyme levels varying with age and sex and pregnancy [10]. Also, the normal serum ALP gradually increases from age 40 to 65, particularly in women. In the present study although the male/female ratio was 38/62, the age interval of the patients was 22-54 years. In other words, the young age may have been the reason for the mild decrease in ALP.

Most commonly, routine laboratory-based coagulation tests which assess the patients' current coagulation status are PT, aPTT, fibrinogen, international normalized ratio (INR), and platelet numbers [30]. The postoperative PT was significantly longer than the preoperative PT in groups F and R. During the anesthetic or surgical procedures, perioperative monitoring of blood coagulation is critical to predict the risk of bleeding.

Conclusion

On the basis of the results of our study, the use of fentanyl, remifentanil as analgesics during TIVA may be considered safe for LFT. However, shorter recovery time in group R and satisfactory postoperative analgesia in the groups F and R suggest that fentanyl and remifentanil may be more appropriate anesthetic choices in these patients. New studies need to be developed to maximize the benefits offered by remifentanil and fentanyl used in the present study.

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